Cancer stem cells generated by alcohol, diabetes, and hepatitis C virus.

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Public Summary:
In summary, alcohol, obesity, and HCV synergistically induce liver tumor development via induction and activation of TLR4 in mice. Pharmacologic inhibition of TLR4 signaling may become a novel therapeutic strategy for HCV-associated liver tumors

Scientific Abstract:
Cancer stem cells (tumor-initiating stem-like cells: TISCs) are resistant to chemotherapy and are associated with metastatic hepatocellular carcinoma (HCC), which is commonly observed in hepatitis C virus (HCV)-infected patients with obesity or alcohol abuse. However, it is unknown whether the TLR4-NANOG pathway serves as a universal oncogenic signaling in the genesis of TISCs and HCC. We aimed to determine whether Tlr4 is a putative proto-oncogene for TISCs in liver oncogenesis due to different etiologies and how Tlr4 is regulated at the transcriptional and epigenetic levels. CD133+/CD49f+ TISCs were isolated using FACS from HCC developed in HCV Core Tg mice fed alcohol, diethylnitrosamine-treated mice, and alcoholic patients with or without HCV infection. CD133+/CD49f+ cells isolated from the animal models and patients are tumorigenic both in vitro and in a xenograft model, and Tlr4 or Nanog silencing with shRNA attenuates their tumor initiating property. Functional oncogene screening of a cDNA library identified the organ size control pathway targets Yap1 and AKT activator Igf2bp3 as NANOG-dependent genes that inhibit transforming growth factor-beta signaling in TISCs. Tlr4 expression is higher in TISCs compared with CD133-/CD49f+ cells. Taken together, Tlr4 may be a universal proto-oncogene responsible for the genesis of TLR4-NANOG dependent TISCs, and this pathway serves as a novel therapeutic target for HCC.